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New Syndrome of Spondylospinal Thoracic Dysostosis With Multiple Pterygia and Arthrogryposis

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We describe a "new" syndrome of spondylospinal thoracic dysostosis with a short curved spine and fusion of the spinous processes, short thorax with "crab-like" configuration of the ribs, pulmonary hypoplasia, severe arthrogryposis and multiple pterygia, and hypoplastic maxilla and mandible in two siblings. This appears to be an autosomal recessive lethal trait. A literature review revealed two reports of four similar or related cases. Am. J. Med. Genet. 69:73–78, 1997.

KEY WORDS: spondylothoracic dysostosis; congenital arthrogryposis; lethal multiple pterygium; maxillary and mandibular hypoplasia; cleft palate; hypoplastic lungs

INTRODUCTION

In a number of skeletal syndromes, there is preponderant involvement of the spinal column and thorax, resulting in short trunk dwarfism mainly due to multiple vertebral segmentation defects, with or without rib anomalies, limb anomalies, or other major organ involvement.

We report a "new" spondylospinal thoracic dysostosis with severe congenital arthrogryposis and multiple pterygia.

CLINICAL REPORTS

Patient 1 was born at 32–34 weeks of gestation following induced labor and forceps extraction because of intrauterine fetal death presumed to have occurred at approximately 7 months in a pregnancy complicated by faint fetal movements. At birth, multiple anomalies were noted. The fetus was hydropic and macerated. Crown rump measurement was 13 cm, crown heel measurement was 19 cm, and head circumference (OFC) was 29 cm. The fetus was in a severely lordotic position. Although relatively large, the head and face were considered normal. The neck was short and wide. The chest was short. The abdomen was protuberant. There were severe contractures of both the upper and lower limbs and overlap of fingers. Five digits were present on all limbs. External genitalia was normal (female). All internal organs, heart, larynx, trachea, lungs, liver, spleen, gastrointestinal tract, kidneys, bladder, uterus, tubes and ovaries, adrenals, pancreas, and thyroid were considered unremarkable. The initial diagnostic impression included "stargazing dwarf" (iniencephaly), severe form of Klippel-Feil sequence, or spondylothoracic dysostosis (Jarcho-Levin syndrome).

Radiographs showed a strikingly short and curved spine. On lateral view, there appeared to be the normal number of vertebral bodies. However, some were misshapen (flattened, wedged, ovoid) or misaligned. There was narrowing of the intervertebral spaces, with fusion of the spinous processes of the cervical, thoracic, lumbar, and sacral vertebrae into a long strip of bone, and a lordotic vertebral curvature (−90°). There were 12 ribs that were crowded together at the vertebral origin and spread out toward the sternal end creating a "crab-like" configuration on anteroposterior (AP) views. The clavicle, scapulae, and long bones of the upper and lower limbs appeared unremarkable, apart from their flexed and adducted position. The skull showed a small maxilla and mandible (Fig. 1a,b).

Patient 2 was born at term by repeat cesarean section and breech presentation. The pregnancy was unremarkable, with ultrasound examination at 4 months showing normal fetal movement and cardiac activity, normal biparietal diameter, head circumference, spine, cord, stomach, bladder, and an anterior placenta. At delivery, she was noted to have similar malformations as

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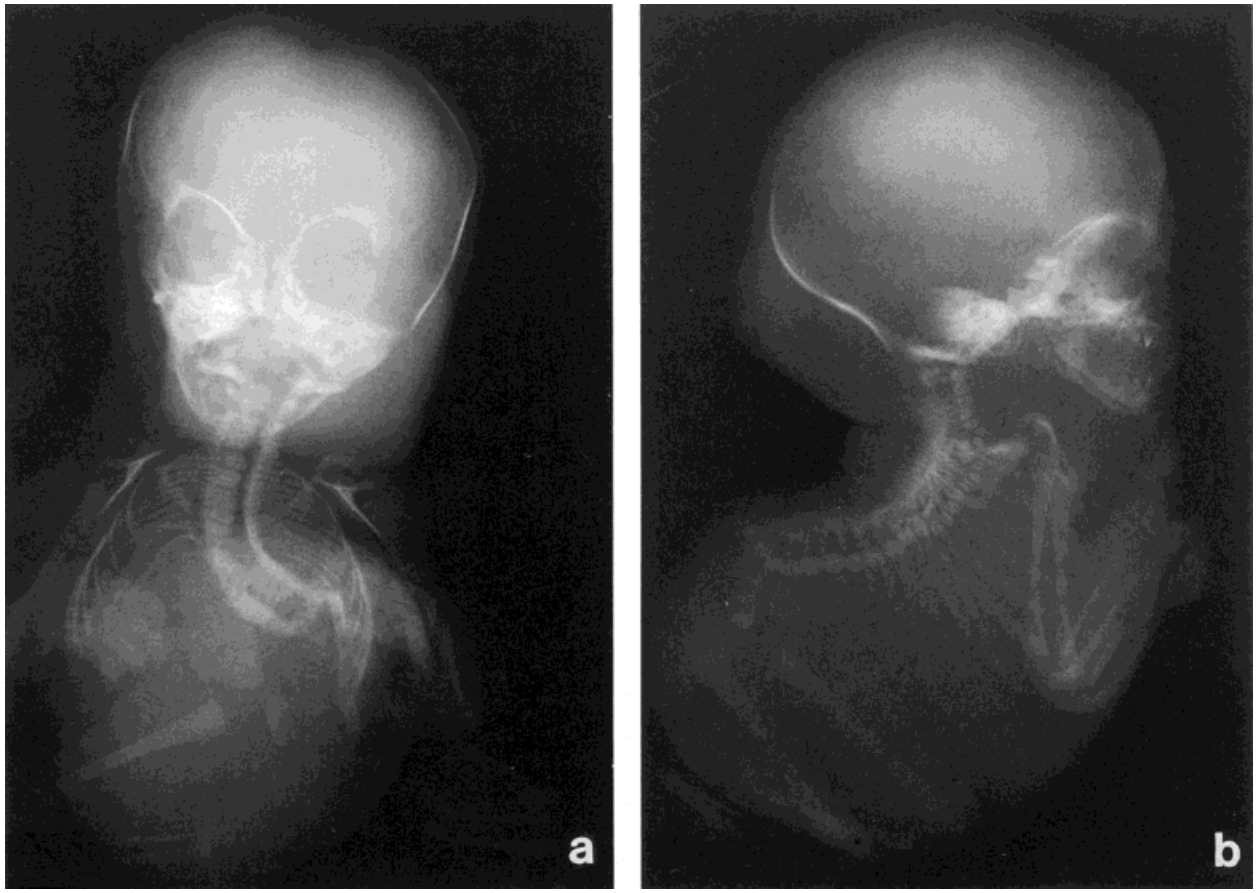

Fig. 1. Anteroposterior (**a**) and lateral (**b**) views of full body radiograph of patient 1.

her sister (patient 1). Her short stiff neck and small chin made attempts at endotracheal intubation unsuccessful. She died soon after.

She had a large head relative to trunk with a round face, flat facial profile, short and wide nose, narrow palpebral fissures with deep-set, small eyes, thin lips with a smooth short philtrum, strikingly small chin, cleft of soft palate, and low-set ears that were posteriorly angulated and cupped. Her neck was so short and wide that her head appeared to sit directly on top of the thorax. The chest was very short and wide, the abdomen distended, and the hips narrow. There was severe lordosis. When viewed from the back, there was a deep horizontal crease behind the neck and also at the junction of the thoracic and lumbosacral areas. The shortness of the spine was evident in the superior displacement of the pilonidal pit, which was surrounded by fairly long hair. There was an increased distance between the anus and the vaginal opening due to a widened perineal body. The limbs were held fixed in flexion and adduction. The lower limbs could not be extended because of the joint contractures at the hips, knees, and ankles. The feet were in an equinovarus position. There was muscle hypoplasia and popliteal pterygium from a fold of skin and soft tissue extending between the mid-thigh to the mid-leg. The upper limbs were also held in flexion and adduction with an antecubital pterygium between the mid-upper arm to the mid-forearm. The wrist was held in flexion with ulnar deviation of the hands. The fingers were flexed with the fingertips closely approximated. There was soft tissue syndactyly between the fingers.

At autopsy (including the brain), there were no apparent internal organ abnormalities. There was pulmonary hypoplasia with a bilateral lung weight of 16 g. There was complete iatrogenic transection of the spinal column and the spinal cord at the thoracolumbar junction. On radiographic examination, the disruption of the spinal column was between T10 and T11. The spinal cord appeared hypoplastic, measuring 0.4 cm in diameter. The spine did not appear as curved on lateral views as that of Patient 1 because of the aforementioned fracture. However, assuming an intact spine, the lordotic curvature was estimated at $-90°$. The spine was short with vertebral bodies that were misshapen and misaligned. The spinous processes were fused into a block of bone. There were 12 ribs that were closely approximated at the vertebral end and fanned out toward the sternal end. There was also a disruption of the spine at C2-C3 as indicated by a gap in the spinous

process. Because of the short neck, the clavicle and the scapulae appeared very high, at the same level as the mandible. The long bones, apart from the adducted and flexed position, were otherwise unremarkable. The pelvic bones appeared normal. The head of the femora were dislocated. The cranium showed a very small maxilla and mandible (Fig. 2a,b).

The mother is gravida 5, para 3, Ab 2, with 1 living child. The first and second pregnancies ended with miscarriages at 8 and 11 weeks. The third pregnancy produced patient 1. The fourth pregnancy produced a normal son delivered by cesarean section. The fifth pregnancy produced patient 2 (Fig. 3a–d).

There is no consanguinity between the parents. The parents are white.

DISCUSSION

With two similarly involved individuals in the sibship, this is presumably an autosomal recessive trait. The parents were given a 25% risk of recurrence. This condition is not likely to be compatible with life. The short small chest associated with pulmonary hypoplasia, and the very short neck and small retrocessed chin occluding the larynx/trachea, are likely to cause respiratory problems. There is also the possibility of deficient innervation of the thoracic intercostal muscles and diaphragm as a factor for respiratory failure at birth.

The most likely abnormality is in a gene that controls development of the spinous processes of the spinal column. The vertebral bodies appear to be discrete hypoplastic structures although sometimes anteriorly displaced or misshapen. However, the spinous processes are densely fused into an unyielding solid block of bone, responsible for the extreme shortness and curvature of the spinal column. Differentiation of the sclerotome is mediated by the neural tube and the notochord, whereas the neural arches and posterior elements are mediated by the neural crest. Because the vertebral body and the neural arches/spine are influenced by different inductive forces, abnormalities of the anterior vertebral body can occur independently of the abnormalities of the spinous processes or vice versa [Morrissy, 1990]. In contrast to previously described cases of spondylothoracic or spondylocostal dysostosis, these two patients have a very striking fusion of the spinous processes and severe lordosis to make this a recognizable and distinct entity.

The short spine results in the ribs being spread out in a “crab-like” configuration rather than assuming the normal parallel placement of individual ribs. This

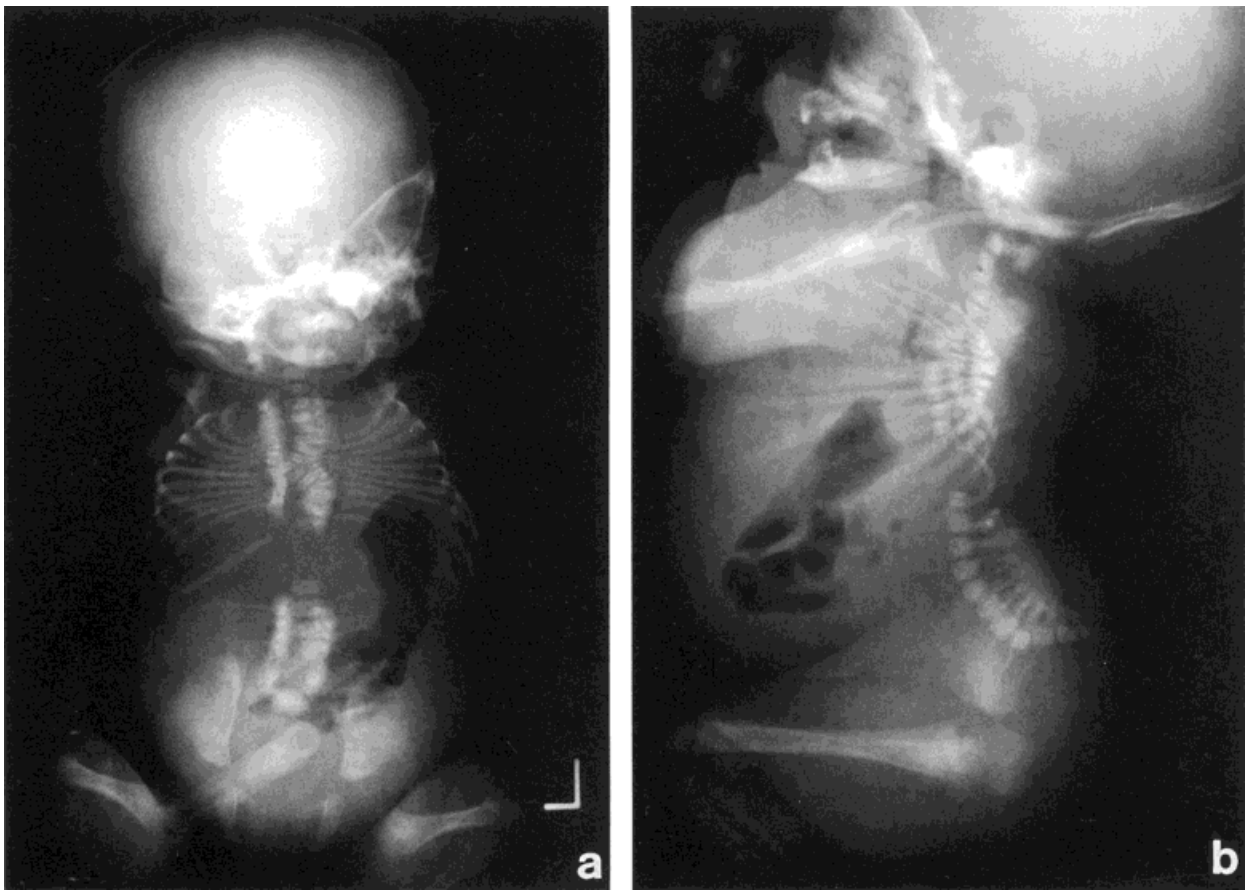

Fig. 2. Anteroposterior (**a**) and lateral (**b**) views of full body radiograph of patient 2.

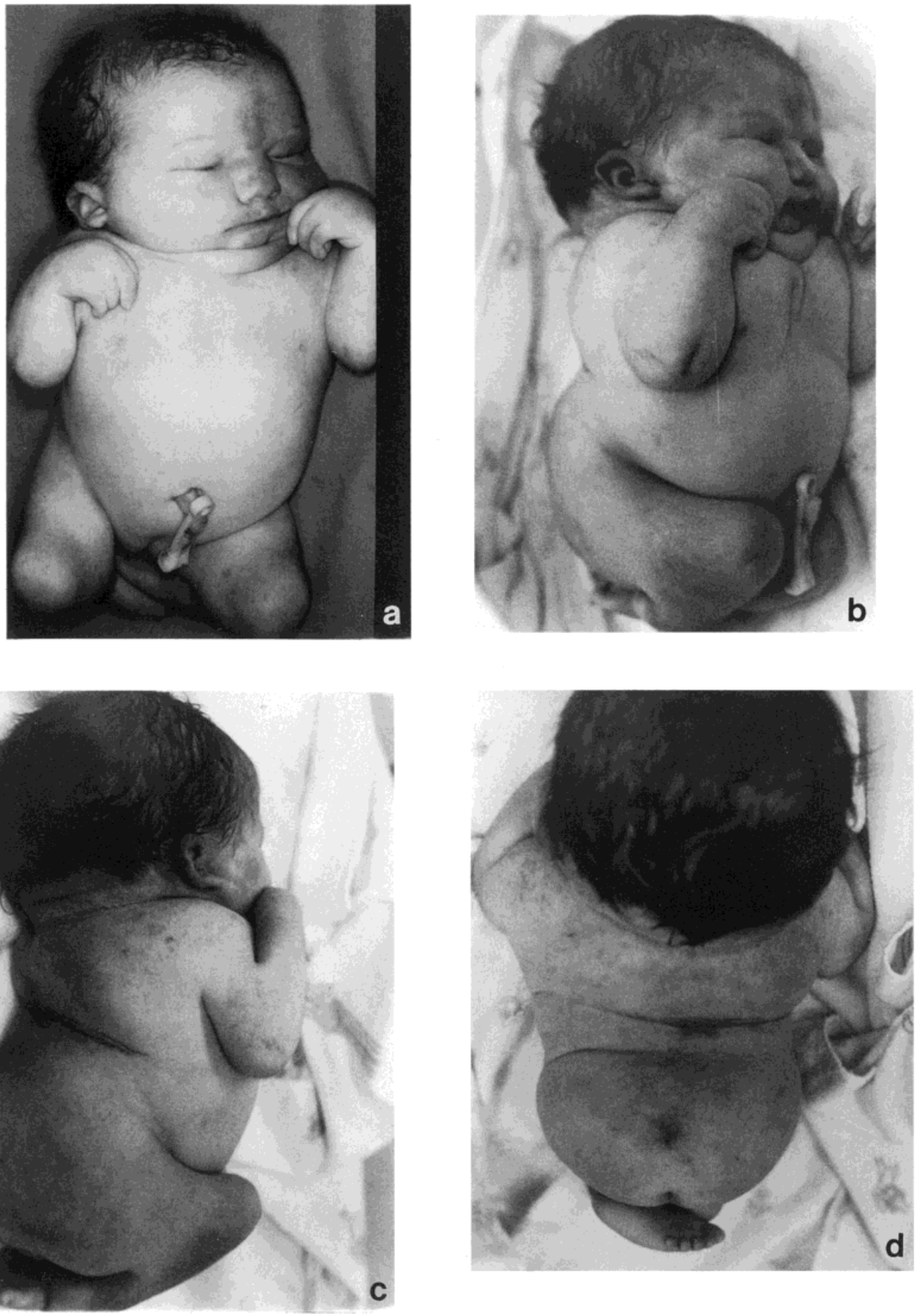

Fig. 3.

results in a short chest cage, high clavicles and scapulae, and short neck. In this respect, these patients are similar to patients with Jarcho-Levin syndrome [Perez-Comas and Garcia-Castro, 1974]. However, in Jarcho-Levin syndrome, the abnormality is more typically a multiple segmentation defect of the vertebral bodies often associated with significant rib abnormalities (abnormally shaped, missing, or fused ribs) and various degrees of kyphosis and scoliosis. In these two patients, the most striking aspects are fusion of the spinous processes with misaligned and misshapen vertebral bodies and the extreme lordosis of the spine, such that the lower thorax and abdomen lie on a horizontal plane. The AP radiologic appearance of patient 1 (Fig. 1a,b) is akin to an AP radiograph of a chicken.

The severe contracture of all limbs is presumably secondary to spinal cord and spinal nerve hypoplasia and compression. There was no apparent brain abnormality, and the spinal cord appeared small. In the absence of CNS function, deficient movement of the limbs could lead to muscle hypoplasia, pterygium of the overlying soft tissue and skin, and joint contractures. Alternatively, a primary cartilaginous/bony fusion is possible. The mother described rolling fetal movements rather than kicking fetal movements. Arthrogryposis and multiple pterygia is a striking finding in these two patients, not described in Jarcho-Levin or other spondylothoracic or spondylocostal dysostoses.

Despite the cesarean section, delivery was very difficult because of the severe arthrogryposis and the inability to pull on legs that would normally extend in the process of delivery. The breech and the flexed thighs and legs had to be delivered as a unit, and the unyielding short curved spine inadvertently fractured in the process.

The spine abnormality is so striking that ultrasonography should allow diagnosis in utero. The normal curvature of spine, with the fetus bent forward, is in striking contrast to the spinal curvature in this condition, with the fetus bent backward. The normal son born between these two patients had a series of ultrasound evaluations throughout pregnancy. However, patient 2 had one ultrasound evaluation at 4 months and, assuming normality, had no subsequent ultrasound follow-up. Presumably, the skeletal abnormality may not be apparent in early mid-trimester and requires sequential examinations to document loss of fetal limb movement and abnormal spinal curvature.

On literature review, there is nosologic confusion in the group of short trunk spondylocostal dwarfism [Ayme and Preus, 1986; Karnes et al., 1991]. The preferred designation is dysostosis (regional or localized malformation) rather than dysplasia (generalized skeletal disorder). Mortier et al. [1996], in a review of 141 patients (115 previously reported and 26 new cases), propose the following three groupings.

1. Jarcho-Levin syndrome—vertebral segmentation defect of the entire vertebral column, "crab-like" rib cage, no major organ involvement, and usually lethal within the first 2 years due to respiratory problems. Most cases have been Puerto Rican (14 of 20 cases) and autosomal recessive.

2. Spondylothoracic dysostosis—multiple vertebral segmentation defects with autosomal recessive intrafamilial variability, death in infancy due to respiratory failure, or survival to adulthood with few symptoms.

3. Spondylocostal dysostosis—multiple vertebral segmentation defects tend to be milder, autosomal dominant, normal life span with variable kyphoscoliosis, low back pain, and decreased spine mobility.

There is radiologic overlap between the latter two groups.

Finally, there is a heterogeneous group, often sporadic, that is difficult to classify. Although the first sibling had a tentative diagnosis of Jarcho-Levin syndrome, the birth of the second affected sibling prompted a more critical review. In Jarcho-Levin, there are vertebral fusions and hemivertebrae causing kyphoscoliosis in addition to the "crab-like" chest cage. There are also severe rib anomalies with fusion and bifurcations. Our patients clearly have a primary bone fusion of the spinous processes of the spinal column with secondary small chest cage, hence our use of the term spondylospinal thoracic dysostosis.

Turkel et al. [1980] describe two similar patients. At birth, both unrelated newborns had cervical hyperextension, severe lordosis, flexion contractures of limbs, popliteal pterygia, cleft of soft palate or high arched palate, and radiographs showing short curved spine with fusion of posterior elements. Both were breech, one delivered by cesarean section. One patient was 7 years old and, despite bilateral femoral osteotomies and intensive physical therapy, had severely limited mobility. Although her speech was impaired, she socialized well. The second patient died within hours due to respiratory failure. On autopsy, the most involved upper spinal column showed small, flat vertebrae and thin intervertebral disks with "nerve roots that were obscured by dense, honey combed, hemorrhagic fibrous tissue that was continuous with and adherent to the dura, arachnoid and periosteum." There was also acute hemorrhage that was assumed to be a perinatal event. They surmise a "selective infectious circulatory etiology" because of febrile illness in one mother and chills in the other early in pregnancy.

Chen et al. [1984] described several cases of lethal multiple pterygium syndrome. Patient 1 (32 weeks) and patient 2 (28 weeks) had multiple pterygium and joint contractures, hypoplastic vertebral bodies, and fused spinous processes, angulated cervicothoracic junction, hypoplastic lungs/heart, and cystic hygroma. They were ascertained because of polyhydramnios or decreased fetal movement and ultrasound examinations showing a cystic mass at the back of the neck. Patient 1 was breech. Patient 2 had a cleft of the soft palate. Both were stillborn 2 to 3 weeks after initial ultrasound examination. Histologic studies showed cartilaginous and

Fig. 3. Frontal (**a**), lateral (**b**), and posterior (**c,d**) views of patient 2. Front and side views show the small retrocessed chin, short neck, and severe arthrogryposis. Side views show the severe lordosis and muscle hypoplasia and pterygium between the thigh and leg and the arm and forearm. Back view shows the deep crease behind the neck and the mid-back, small hips, and the superior displacement of the pilonidal pit, marking the caudal end of the spinal column.

bony fusion of the spinous processes and fusion of the epiphyseal cartilage of the elbow and ulna.

It seems reasonable to speculate that the patients described by Chen et al. could represent an earlier phase of this syndrome that later progresses to the stage described in our patients and in Turkel's patients. Although cystic hygroma was not noted in our patients, the regression of cystic hygroma with advancing gestation, as in Turner syndrome, is well recognized. This condition could well be a distinct entity that is recognizable from among lethal multiple pterygium/cystic hygroma cases.

The phenotype of these two siblings is so striking that it should be considered a distinct autosomal recessive malformation syndrome of spondylospinal thoracic dysostosis characterized by very short lordotic spinal column with bony fusion of the spinous processes, "crab-like" small rib cage, congenital arthrogryposis and multiple pterygia, and pulmonary hypoplasia. Although most patients die prenatally, there is the prospect of term birth and rare survival with severe physical disability.

REFERENCES

Ayme S, Preus M (1986): Spondylocostal/spondylothoracic dysostosis: The clinical basis for prognosticating and genetic counseling. Am J Med Genet 24:599–606.

Chen H, Immken L, Lachman R, Yang S, Rimoin DL, Rightmire D, Eteson D, Stewart F, Beemer FA, Opitz JM, Gilbert EF, Langer LO, Shapiro LR, Duncan PA (1984): Syndrome of multiple pterygia, camptodactyly, facial anomalies, hypoplastic lungs and heart, cystic hygroma, and skeletal anomalies: Delineation of a new entity and review of lethal forms of multiple pterygium syndrome. Am J Med Genet 17:809–826.

Karnes PS, Day D, Berry SA, Pierpont ME (1991): Jarcho-Levin syndrome: Four new cases and classification of subtypes. Am J Med Genet 40:264–270.

Morrissy RT (1990): "Pediatric Orthopedics." 3rd ed. Philadelphia: J.B. Lippincott, p 6.

Mortier GR, Lachman RS, Bocian M, Rimoin DL (1996): Multiple vertebral segmentation defects: Analysis of 26 new patients and review of the literature. Am J Med Genet 61:310–319.

Perez-Comas A, Garcia-Castro JM (1974): Occipito-facial-cervico-thoracic-abdominal-digital dysplasia: Jarcho-Levin syndrome of vertebral anomalies. J Pediatr 85:388–391.

Turkel SB, Iseri AL, Fujimoto AO (1980): Malformation complex spondylohypoplasia, arthrogryposis and popliteal pterygium. Am J Dis Child 134:42–45.